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Insights into the genetic basis of retinal detachment

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Abstract

Retinal detachment is a serious and common condition, but genetic studies to date have been hampered by the small size of the assembled cohorts. In the UK Biobank dataset, where retinal detachment was ascertained by self-report or hospital records, genetic correlations between retinal detachment and high myopia or cataract operation were respectively 0.46 (SE=0.08) and 0.44 (SE=0.07). These correlations are consistent with known epidemiological associations. Through meta-analysis of genome-wide association studies using UK Biobank retinal detachment cases (N=3977) and two cohorts, each comprising ~1000 clinically-ascertained rhegmatogenous retinal detachment patients, we uncovered 11 genome-wide significant association signals. These are near or within *ZC3H11B*, *BMP3*, *COL22A1*, *DLG5*, *PLCE1*, *EFEMP2*, *TYR*, *FAT3*, *TRIM29*, *COL2A1* and *LOXL1*. Replication in the 23andMe dataset, where retinal detachment is self-reported by participants, firmly establishes six retinal detachment risk loci: *FAT3*, *COL22A1*, *TYR*, *BMP3*, *ZC3H11B* and *PLCE1*. Based on the genetic associations with eye traits described to date, the first two specifically impact risk of a retinal detachment, while the last four point to shared aetiologies with macular condition, myopia and glaucoma. Fine-mapping prioritised the lead common missense variant (TYR S192Y) as causal variant at the *TYR* locus and a small set of credible causal variants at the *FAT3* locus. The larger study size presented here, enabled by resources linked to health records or self-report, provides novel insights into retinal detachment aetiology and underlying pathological pathways.

Introduction

The UK Biobank is a major international research resource designed to help identify the genetic and non-genetic causes of complex diseases burdening middle and old age (1). Data linkage to the UK National Health Service (NHS) hospital in-patients records, achieved for a large portion of the 500,000 participants, makes it particularly valuable for the investigation of a wide range of conditions. Here, we made use of the UK Biobank to gain genetic insight into retinal detachment (RD), a common condition and cause of emergency ophthalmic intervention.

The processes leading to the vision-threatening separation of the neurosensory retina from the underlying retinal pigment epithelium can be diverse. Break in the retina leading to sub-retinal penetration of vitreous humour characterises the most frequent RD type, hence called rhegmatogenous (RRD). Other forms exist: the far less common tractional form, with no detectable retinal break, and the very rare serous RD, caused by inflammatory or exudative retinal conditions (2).

Annual incidence has been estimated for RRD at 12 per 100,000 population (3) in the UK, peaking in individuals in their sixties (4). Posterior vitreous detachment, a common age-related condition, is thought to be a frequent initiating event (5, 6). Trauma, cataract operation, myopia and diabetic retinopathies can precipitate vitreous changes (5) and have all been associated with increased risk of RD. Retinal conditions such as lattice degeneration (7, 8) may predispose to retina breaks (holes and tears). Most epidemiological studies have also reported RD incidences to be 1.3 to 1.9 fold higher in men (3, 9, 10), even when trauma cases are excluded (10, 11).

RD has been poorly characterised genetically due to the small sample sizes of collections assembled. A genetic predisposition for RRD has been suggested by

family studies, with roughly a doubling of lifetime risk in first degree relatives of cases compared to that of controls (12, 13), and by the, rare, Mendelian syndromic conditions featuring RRD (14, 15). The proportion of RRD liability contributed by common genetic variants was estimated at 27% in the very first RRD genome-wide association study (GWAS), which we performed using 867 Scottish cases (16). This GWAS led to the identification of a common coding variant in the *CERS2* gene, rs267738, as significantly associated. Several rare mutations in *COL2A1* (in which Stickler syndrome causal variants have been described) have been implicated in familial dominant RRD (17, 18). A burden of rare variants in this *COL2A1* gene as well as a common intronic variant, rs1635532, have additionally recently been suggested to contribute to idiopathic RRD (19).

Here, we evaluate genetic associations with retinal detachment risk, leveraging available information in the UK Biobank. The data linkage to hospitalisation records should allow identification of retinal detachment (RD) cases, with some details. In addition, all UK Biobank participants completed, at recruitment, a touchscreen questionnaire followed by verbal interviews which included history of retinal detachment. This allows capture of potential cases not linked to medical records. This ascertainment is *a priori* less precise than the hospital records linkage. However, RD, requiring surgical intervention, appears to be a significant ophthalmic event that has a memorable impact on patients (12).

To validate the retinal detachment cases ascertained from UK Biobank, we first assessed self-reported RD using the overlap with hospital admission records where possible, together with the wealth of other information gathered on participants. We then performed a genome-wide association study (GWAS) of RD in the UK Biobank using the union of self-reported and hospital record linked cases, to maximise power

in a sample of RD cases anticipated to be aetiologically heterogeneous. To interpret the genetic associations uncovered, we carried out sensitivity analysis using phenotypic subsets, and sought out overlapping associations with high myopia and cataract operation, two well established conditions increasing RD risks, as well as with clinically ascertained RRD in independent sets from Scotland and England.

Finally, we performed the largest GWAS analysis to date for retinal detachment by combining the UK Biobank RD data with the, smaller, studies of clinically ascertained RRD. To replicate our findings, we performed a look-up, in a population-based sample from the personal genetics company 23andMe, Inc. data, for the lead variants of the genome-wide significant signals (study workflow is summarised in Fig S1).

Results

Evaluation of UK Biobank self-reported retinal detachment

A total of 1754 UK Biobank participants self-reported retinal detachment (RD-SR) at any one of the three assessment visits. Questionnaire responses were fairly consistent in the baseline visit, with 88% of RD-SR cases also indicating a condition which would prevent them from undergoing spirometry. This compares to 7.7% in all respondents (history of retinal detachment is one of the contra-indications for spirometry in the UK Biobank protocol). Furthermore, 79.4% of cases reported having had an eye problem other than wearing glasses (compared to 14.7% in all respondents), and 79.8% answering as having had a retinal operation/vitreotomy operation (compared to 0.6% in all UK Biobank participants).

RD-SR cases display significant distributional shifts compared to controls (Table 1), with magnitudes consistent with RD epidemiological reports. They were older (median year of birth 1947 compared to 1951 in controls) and with a 1.3 times greater proportion of men (59.1 % compared to 45.1%). Over a quarter had had a cataract operation, in line with prior cataract surgery reported in a fifth to a third of individuals with RD in European cohorts (3, 9, 20, 21). Other self-reported conditions of significant increased prevalence compared to controls include ocular trauma, diabetes, macular degeneration and glaucoma. The distributional shifts are not due to sex bias, as they are maintained in the same gender comparisons (Table1), for example for eye trauma, significantly more frequent in men (P -value =0.012). When applicable, the median age for first use of lens to correct for myopia was younger, 12 years old, in cases compared to that in controls, 17 years old. This self-reported fact has been shown to accurately identify myopia, and age at first use to inversely correlate with severity of myopia (22). The shift observed in RD-SR cases towards younger age of onset therefore suggests higher incidence of high myopia, in agreement with it being a well-recognized risk factor for RD (3, 11, 23).

Linkage to “retinal detachment or break” in hospitalisation records was found for 890 (50.7%) of the RD-SR cases (Table S1). The highest proportion (~half of those linked to a record, ~25% of total RD-SR cases) corresponded to RRD, ICD10 code H33.0 (retinal detachment with retinal break). However, very surprisingly, almost as many of the RD-SR cases (~21%) were linked to the hospital record H33.2, which represents exudative (serous) retinal detachment, a very rare form of detachment, suggesting that the ICD sub-code entries are likely to be inaccurate. The ~11% of RD-SR cases linked to an H33.3 code (retinal break, no detachment) could also reflect imprecise coding in hospital entries and/or that the breaks are a risk for future

retinal detachment. Fig 1 displays retinal detachment ICD9 and ICD10 entries in the overall UK Biobank participants and illustrates the overlaps between the different sub-codes, across hospitalisation events.

There seems little gain in restricting RD-SR cases to the individuals who self-report a retinal operation/vitreectomy for greater accuracy: 363 cases would be excluded, but these do not change the overall characteristics of the RD-SR cohort (Table 1 and S1). Given the enrichment in RD cases that they are likely to represent, we combined RD-SR cases with individuals linked to the ICD10 super code H33 and ICD9 code 361 to increase power in the initial association study (RD-SR-ICD).

Genetic variants enriched in the UK Biobank SR and ICD-defined retinal detachment cases

GWAS was carried out in the UK-Biobank subset of participants of white-British ancestry. It identified three genome-wide significant signals with common lead variants rs11992725 (MAF=31.9%, P-value= 3.1×10^{-10}) on chromosome 8, an intronic variant in *COL22A1*, rs7118363 (MAF=39.2% P-value= 1.2×10^{-16}) on chromosome 11, an intronic variant in *FAT3* and rs633918 (MAF=38%, P-value= 1.6×10^{-8}), an intronic variant in *GRM5* (Fig S2 and regional plots Fig 2A).

No genome-wide significant association has so far been published for the *COL22A1* lead variant (or with 1000G proxy variants in high LD, $r^2 > 0.6$) in the GWAS Catalog or using Phenoscanner (24), as of September 2019. Only recently, the lead variant in *FAT3* has been associated with heel bone mineral density (25) using the UK Biobank dataset (N=194398, P-value= 4.65×10^{-8}). The lead variant in *GRM5* is in LD

with variants that have been strongly associated with eye colour (e.g. proxy rs7120151, $r^2=0.64$ $D'=0.94$, $P\text{-value}=2.45\times 10^{-10}$) (26).

A full list of loci with lead variants displaying an association $P\text{-value} < 5\times 10^{-6}$ is shown in Table S2. Two of the 24 suggestive loci ($5\times 10^{-6}<P\text{-value}\leq 5\times 10^{-8}$) are amongst the most strongly supported loci associated with common myopia (27): *LAMA2* (identical lead variant) and *BMP3* (reported myopia lead variant rs5022942 (27) in some linkage disequilibrium, $r^2=0.19$, $D'=0.999$, with the RD suggestive locus lead variant). Another notable suggestive association is that within the *COL2A1* gene as it is an excellent RD candidate gene (18). The *COL2A1* common variant rs1635532 previously proposed to be associated with RRD (19) displays no association ($P\text{-value}=0.95$) in the UK Biobank RD-SR-ICD, whilst in low linkage disequilibrium with the suggestive lead variant, rs1635554 ($r^2=0.15$, $D'=0.88$). The *CERS2* variant rs267738 previously associated with RRD (16) shows nominally significant association, $P\text{-value}=4.2\times 10^{-3}$, with the major T allele increasing risk as previously reported.

The quantile-quantile plot for the GWAS results (Fig S2- $\lambda_{GC}=1.097$), and the LDscore regression intercept close to 1 (1.0083, $SE=0.0067$)(28), suggest an excess of genetic associations attributable to polygenic effects, compared to the null expectation of no genetic effect. Using a more balanced, 1:3, case:control design, that has been advocated (29) to avoid possible distortion of results for rare variants (which are not analysed here), yields the same top two genome-wide significant signals but with less significant $P\text{-values}$ (Fig S3), indicating some loss of power when using a smaller set of control genomes.

Jointly, the common variants tested contribute a heritability on the liability scale, h_{gl}^2 , of 0.23 (P-value= 2×10^{-72}). h_{gl}^2 calculated using LD score regression was similarly low but significant, 0.1378 (SE=0.0194).

Retinal detachment sub-analyses and genetic overlaps with high myopia and cataract operation in the UK Biobank dataset

We carried out sensitivity analyses to tease out phenotypic heterogeneity. Performing the same GWAS analyses after removing cases linked to an ICD code suggesting a break in the retina but no detachment (Fig. 2B, leaving Ncases=2893 for Ncontrols=360,233) did not change the effect sizes of the *COL22A1* and *GRM5* lead variants substantially (Table S3). The estimated effect for the *FAT3* lead variant, OR=1.157, remained significant but fell just outside the 95% CI of that obtained in the full analysis [1.158,1.265] (Table S3). This suggests that the subset of cases with breaks may contribute more substantially to the *FAT3* signal.

Performing GWAS in the much reduced set comprising only the cases linked to an H33.0 ICD code (Ncases=1380 and Ncontrols=360,233) – which should correspond most closely to RRD cases - does not yield any genome-wide significant associations. However, *FAT3* remains amongst the strongest signals (P-value= 8.6×10^{-7} for lead variant rs10765567) (Fig 2C).

In addition to ICD codes sensitivity analyses, we looked for evidence in UK Biobank of shared genetic signals with the two epidemiologically established conditions known to significantly increase retinal detachment risk: cataract operation and high myopia. GWAS analyses for high myopia (Ncases=2737 and Ncontrol=47,635) and

history of cataract operation (Ncases=21679 and Ncontrols=387,283) showed contribution of genetic variants to risk, very strong for high myopia, with LD score regression estimated SNP-based heritabilities, h_{gl}^2 , of 0.7217 (SE=0.0642), and very modest 0.0719 (SE=0.0072) for cataract operation. Manhattan plots for these analyses are shown in Fig S4 A-B, and the lists of significantly associated loci in Table S4-S5. In addition to the top associated locus, intergenic *GOLGA8B-GJD2* (lead rs524952, P-value=1.2x10⁻²⁴), nine out of the other sixteen high myopia loci show nominal association with RD-SR-ICD ($P_{RD} < 0.05$). All ten associations show agreement with the epidemiological association (the allele increasing high myopia risk increases risk of retinal detachment). Two out of the 20 cataract operation associated loci, encompassing the eye colour genes *OCA2* and *NPLOC4*, show nominally significant association with RD, with the cataract risk allele increasing risk of retinal detachment. The regional high myopia and cataract association plots for the three genome-wide significant retinal detachment loci *COL22A1*, *FAT3* and *GRM5* are shown in Fig S5 and suggest that those are not driven by a high myopia or cataract association.

Consistent with the epidemiological and phenotypic associations, the overall genetic correlations calculated using LD score regression slopes (30) were significant, 0.46 (SE=0.08) between RD and high myopia, 0.44 (SE=0.07) between RD and cataract operation, whilst 0.25 (SE=0.066) between high myopia and cataract operation.

Validation of UK Biobank RD genetic associations in datasets with clinically ascertained RRD cases

Genetic variants associated with RD-SR-ICD in the UK Biobank were evaluated for their association with clinically ascertained RRD in two independent datasets. Those were small datasets comprising 980 and 1184 cases, collected in Scottish vitreoretinal surgeries and at the Moorfields London Hospital respectively. We performed GWAS scans using these clinically ascertained cases and population matched controls (N=9,706 from Scotland and N=10,000 from London), and genotypes imputed to the same Haplotype Reference Consortium (HRC.r1-1) reference panel as that used for UK-Biobank dataset (data clean up Supplementary methods 1 and 2).

Association statistics for the lead variants of the three RD-SR-ICD genome-wide significant loci are displayed in Table S6. The *FAT3* signal lead variant shows consistent effect direction and magnitude across studies (low heterogeneity index, $I^2=0$, P-value=0.56), with estimated OR for the major allele varying from 1.111 (RRD-London) to 1.186 (RD-SR-ICD). Effect directions at the two other genome-wide significant loci were consistent across all datasets, but heterogeneity in their magnitude was high although not significant ($I^2=64\%$, P-value=0.06 for COL22A1 lead variant, $I^2=59.7\%$, P-value=0.084 for GRM5's), indicating OR 95% CI overlap between the three studies.

Furthermore, using summary statistics from the latest, large-scale, refractive error GWAS (31), we evaluated the effect of a myopia genetic risk score on retinal detachment risks in the two types of case ascertainment. The score distributions showed a similar shift toward higher scores for cases in both the UK Biobank study

of non-clinically ascertained RD and the dataset of clinically ascertained RRD (Fig S6). The myopia genetic score effects on RD risks were of similar magnitudes in both datasets, with significant increase of RD risk, $OR_{rd}=1.711$ ($CI=[1.518;1.928]$, $P\text{-value}=1.39\times 10^{-18}$) and $OR_{rrd}=1.598$ ($CI=[1.387;1.840]$, $P\text{-value}=8.12\times 10^{-11}$), in individuals in the highest quintile of the myopia genetic risk score relative to individuals in the lowest quintile (Fig 3). The corresponding odds ratio for high myopia risk in UK Biobank participants was 3.444 ($CI=[2.987;3.970]$, $P\text{-value}=4.6\times 10^{-65}$).

Supported by this range of evidence of common genetic underpinning, a GWAS meta-analysis for all studies (GWAMA) was performed. Of note, the *CERS2* variant rs267738 we previously reported as associated with RRD (16) did not reach nominally significant association with RRD in the analysed London-based dataset (which only partially overlaps with the London-based dataset used previously (16)), allele T increasing risk, $OR=1.023$ ($CI[0.925-1.132]$, $P\text{-value}=0.65$), despite good quality calls for a genotyped variant in high LD with it, rs267734, on the Illumina GSA chip used here.

GWAMA of UK Biobank and clinical retinal detachment datasets

Following GWAMA and removal of variants with high heterogeneity across studies, 239 variants distributed across 11 independent loci showed genome-wide significant ($P\text{-value} < 5\times 10^{-8}$) association with retinal detachment (Fig 4 ; Fig S7 and Table S7 for lead variant regional plots and summary statistics). These loci include *FAT3* and *COL22A1*. *TYR* is also included, not the physically close *GRM5*, with the common missense variant rs1042602 (*TYR* S192Y) as lead variant. The A derived allele,

strongly associated with light skin colour (32) and absence of freckles (33), increases the risk of retinal detachment in all three studies, with high homogeneity (Forest plot Fig S8). In addition, the 5' *COL2A1* locus, upstream of the known familial RRD causal gene *COL2A1*, as well as *BMP3*, 5' *ZC3H11B*, *DGL5*, 5' *EFEMP2*, *PLCE1*, *LOXL1* and an intergenic region between the *TRIM29* and *OAF* genes are also genome-wide significant. The GWAMA had a genomic control inflation factor, λ_{GC} , of 1.096 and the LD score regression indicates the inflation of type 1 errors to be due mostly (~85%) to true genetic effects (intercept = 1.0186 (0.0069), ratio = 0.152(0.056)).

The Functional Mapping and Annotation of genetic association (FUMA) tool (34) was used to annotate the GWAMA results. It called heuristically two independent lead variants at the *BMP3* locus, rs28420618 and rs74764079, based on low level of LD ($r^2 < 0.1$) between these two physically close genome-wide significant variants. A stepwise model selection, implemented in GCTA (35), indicated association at each of the eleven loci to be captured wholly by the variant with the lowest P-value. Further conditioning on each of these lead variants demonstrated that the lead variant effectively tags all of the association signal at each locus, except at *BMP3*. There, conditional analyses suggested two signals, none of which reaching genome-wide significance on its own, tagging each other to some extent, and represented by the independent lead variants detected by FUMA (Table S8 and Fig S9). The same two signals underlie genome-wide significant associations at *BMP3* in the recent, large-scale, refractive error GWAMA (31).

Further statistical delineation of credible sets of causal variants was carried out following the method described by Mahajan et al (36) (see methods). Results, shown

in Table S9, point to one variant with high causal probability ($PIP > 0.6$), the *TYR* lead variant, rs1042602, and to a small credible set of variants for the *FAT3* signal, encompassing the lead and three linked variants. An alternative variant selection method implemented in FINEMAP(37) was applied to the denser RD-SR-ICD GWAS and resulted in prioritisation of a very similar sets of variants at *COL22A1* and *FAT3* (Table S10).

FUMA annotated a total of 472 candidate causal variants, the 12 independent lead SNPs and all tagged ($r^2 > 0.6$) variants. Those with distinctive functional annotations are listed in Table S11. Two loci harbour variants predicted to have highly deleterious effect (CADD score > 20) (38): the missense and lead variants in *BMP3* (rs74764079) and in *TYR* (rs1042602). High CADD scores (> 15) for variants in high LD with lead variant were also notable in *TRIM29*, *COL2A1*, *PLCE1* and *LOXLI*. Evidence of potential transcriptional regulatory attributes could be found at each of the 11 loci (Table S11); for example for every variant of the small credible set established at *FAT3*.

Table S12 lists previously reported associations, or top associations in UK Biobank PheWAS repositories (Phenoscaner, Global Biobank Engine or Gene Atlas), for the lead SNPs, all of which except lead at *DGL5*, are amongst the top likely causal variants. In addition to the associations to myopia and refractive error already noted, these look-ups highlighted ocular axial length (and height) association for the lead variant in 5' *ZC3H11B*, and retinal macular thickness for the lead, high CADD and highly likely causal *TYR* missense variant.

Gene-based association analysis (Table S13) pointed to two additional associated loci, *CMSS1* and *C16orf45* or nearby **RP11-1021N1.1**. Transcriptional expression in

human eye tissues (Table S14) shows that many implicated genes, encompassing those defined using the SNP2GENE function in FUMA (N=102, see METHODS) and the three genes highlighted by the gene-based test, are highly expressed in the retina (neuronal retina or retinal pigmented epithelium). Of note two GWAS loci have a very limited number of candidate target genes: *COL22A1* is the sole gene at the corresponding locus, and *FAT3* together with a gene on another chromosome, *DBI*, implicated by trans-eQTL effect of lead variant in a brain expression dataset, at the *FAT3* locus. Mouse mutations associated with abnormal retinal morphologies have been described in four genes, located at independent loci: *TYR*, *FAT3*, *C4orf22* and *COL2A1* (Table S14).

Gene-set analysis, with the genes prioritised from variants at a permissive GWAS P-value threshold of 10^{-5} , shows “basement membrane components” as top enriched GO cellular-component pathways ($P_{\text{enrichment}} = 6.9 \times 10^{-3}$) with included genes *EFEMP2*, *COL2A1*, *LOXL1*, *EFEMP1*, *COL8A1*, *FRAS1*, *LAMA2* and *ACHE*, from independent GWAS loci. The trait-GWAS enrichment (GWAS Catalog e96 2019-05-03), extends overlap with refractive error, myopia, macular thickness and axial length GWAS results (Table S15). Five genes (*DUSP12*, *BACS3*, *BMP2*, *COL8A1* and *PLCE1*), each at independent RD loci, were in addition flagged as overlapping with the glaucoma endophenotype, vertical cup to disk ratio GWAS gene-set.

Replication in 23andMe dataset

Replication was sought for the eleven variants capturing association signals at the genome-wide significant GWAMA loci by performing association analysis in the large, independent, 23andMe dataset. In this dataset, the 9171 RD participants of

European ancestry analysed were self-reported according to questionnaire administered on a web-based interface. Six associations, at *ZC3H11B*, *BMP3*, *COL22A1*, *PLCE1*, *TYR* and *FAT3* replicate at a Bonferroni corrected significance threshold of 0.0045 ($P\text{-value}=0.05/11$) (Table 2). In all the eleven look ups, the alleles associated with increased retinal detachment risk were the same as in the GWAMA, and all corresponding odds-ratio 95% CI overlaps or are very close to each other (Table 2). Alternative variants tagging the lead variants at each loci were checked post-hoc, to account for potential genotyping quality issues, with similar outcomes (Table S16)

Discussion

We explored the use of cases ascertained from a population Biobank for the study of retinal detachment. Genotypes from study volunteers with self-reported conditions or linked to medical records are becoming increasingly available to researchers, yet, to our knowledge, have never been evaluated for the study of RD.

For a number of conditions, self-report has been shown to be specific, while possibly lacking in sensitivity (22, 39). Our findings support this to also be the case for RD with the RD self-reported participants in UK Biobank displaying characteristic features well-established for this condition. A more thorough investigation of phenotype accuracy is however warranted, especially with linkage to medical and operation notes increasingly available. With genetic risk effect sizes for common conditions typically small (41), self-reported conditions have the potential to boost power of genome-wide association studies (39, 40). For example, the recent large refractive error GWAS (31) exploited the remarkable similarity of genetic findings

between analyses of refractive errors derived from a simple online questionnaire, and those derived from optical instruments (40).

A major limitation of our work is that while case numbers have been increased by using the UK Biobank dataset, we are unable to ascertain which retinal detachment subtypes the cases developed. We did flag that the hospitalisation records ICD sub-codes may be imprecise. The percentage of RD cases sub-coded as H33.2, which represents serous retinal detachment, was far greater than clinical experience would suggest. Supporting a widespread systematic error with regard to this specific code, seven individuals recruited for the Scottish RRD study were also volunteers for the Scottish population-based GS:SFHS study and all allocated H33.2 in the extracted hospitalisation records (two had also the H33.0 code at another hospitalisation episode). These seven individuals were definitively phenotyped as RRD by consultant surgeons. This error is likely due to erroneous entries, as further subtypes of H33.0 do exist in the classification of diseases, including H33.02, retinal detachment with multiple breaks. However, the linked H33 records have only 1 digit after the dot. The increased frequency of individuals linked to the H33.3 subtype, corresponding to break in the retina but no detachment, amongst UK Biobank participants who self-reported a retinal detachment compared to controls (11% versus 0.14%) could again reflect erroneous coding, but is also consistent with a break being a precursor of future RD. The hierarchical structure of diseases in the ICD classifications, exploited by others to improve detection of genetic associations (41), should ensure some degree of specificity. All these considerations justified our combination of all H33 codes for the purpose of our initial analysis, which aimed at identifying genetic factors predisposing to retinal detachment risk.

The SNP-captured heritability estimate for RD in the UK Biobank, 23%, appears very similar to that obtained, using the same method, for RRD in the Scottish clinical dataset (16). Furthermore, the very identical effects of a genetic load of known myopia risk variants on the UK Biobank RD and clinically-validated RRD risks supported that these datasets could be combined to increase risk variant detection. Close to 6000 retinal detachment cases were analysed in the GWAMA, with some very consistent effects across sets. Smaller datasets, such as those analysed so far for clinically-validated retinal detachment, are prone to false negative as well as “winners curse”, in which effect sizes reported are upwardly biased (42).

Association with retinal detachment was replicated for six genome-wide significant lead SNPs in an independent dataset, 23andMe, where definition of cases was entirely self-reported. It is noteworthy that p-values in the replication were generally less significant than in the GWAMA, despite a larger number of cases: this could be due to a looser phenotype definition, a web-based setting, some degree of curation of our controls based on ICD codes and self-reported vitreo-retinal surgery, younger median age of participants so that controls could be cases at older age with higher probability, or analysis method. The 23andMe analysis used a logistic regression method that may be less powerful in large sample size study than the linear mixed model approach (43).

Many of the GWAMA implicated genes have functions very pertinent to retinal detachment aetiologies. There was a clear myopia-related genetic load, in line with expectation. High myopia is the strongest retinal detachment increasing risk factor in individuals who have undergone cataract operation, above the type of cataract surgery or history of trauma (11). Myopia is also a prominent feature in ~50% of cases who have never undergone cataract operation (3, 44). RD onset under the

age of 50 years old is strongly associated with high myopia (11, 20, 23). Risk of chorio-retinal abnormalities and posterior retinal detachment, often but not always associated with a retinal break, increases with the severity of myopia and greater axial length (45-48). This is a cause for concern, as myopia and, concomitantly, high myopia are showing significant increases in global prevalence (49). Whilst findings of myopia genetic risk factors are not surprising, not all myopia loci may confer increased RD risk, thus informing on myopia, itself a heterogeneous condition. For example the lead high myopia variant at *PRSS56* (OR =1.3, CI=[1.218-1.397]) displayed no significant risk for RD. The loci containing genes relating to increased elongation of the eye and basal membrane remodelling are likely to be most relevant to RD. One of the six replicated RD loci, 5' of *ZC3H11B*, is a newly identified refractive error locus (31) and has been associated with ocular axial length (50) and high myopia (51).

In agreement with a Dutch familial aggregation study (12) suggesting that RRD genetic risk must extend beyond that contributing to myopia risk, at least two of the replicated RD loci, *FAT3* and *COL22A1*, did not appear to exert their effect on RD primarily through myopia, nor through cataract operation. Our fine-mapping analysis highlighted a small set of causal variants at the *FAT3* locus, including the lead variant which was also recently associated with heel bone mineral density(25). *FAT3* encodes an atypical cadherin. Its pattern of expression is wide, but its role in the retina is well established in mice. Mice homozygous for a knock-out allele exhibit abnormal neuronal retina, with an additional synaptic layer (52). It is possible that this altered structure would make the retina more prone to breakage, in keeping with the suggestion from the GWAS sensitivity analyses that *FAT3* may be especially concerned with the retinal breaks. *COL22A1* appears to be the only candidate target

gene at the corresponding locus and encodes for the collagen, type XXII, alpha 1 chain, a basement membrane collagen with a very restricted pattern of tissue expression (53). It is highly expressed in the retina (mouse and human tissues) where its function is completely unknown. Its role in extra-cellular matrix adhesion has been advanced in myotendinous junction, following knockdown of COLXXII expression in zebrafish resulting in contraction-induced muscle fiber detachment (54). Remarkably no association has been reported so far for the implicated variants.

The *TYR* and *PLCE1* associations point to retina structure and homeostasis, impacting ocular conditions not limited to RD.

Fine-mapping prioritized the *TYR* association to be driven by the missense variant pS192Y, lead variant in a recent retinal macula thickness GWAS (55). It is likely to act through variation of tyrosinase in the retinal pigmented epithelium (RPE), the single cell layer of polarised cells that plays a crucial role in maintenance of the neural retina. While a large epidemiological study on prevalence of RRD in albino patients, whose tyrosinase is inactive, is unavailable, patho-physiologies that may concur with retinal detachment have been discussed (56). Histological eye sections of mice with an allelic series at the *Tyr* locus strongly suggest that albino adult mouse retinas are prone to detach compared to wild type mice (57). Abnormal morphology of the RPE cells and impaired communication between the RPE and neuronal cells, affecting retinal ganglion cell development, have been well documented in albino mouse embryos (58). Compromised gap junctions between RPE and neural retina represents a compelling cause for retinal detachment risk.

The *PLCE1* RD lead variant is in LD ($r^2=0.6$, $D'=1$) with the reported lead variant for optic nerve cup to disk ratio, a glaucoma endophenotype (59), and in complete LD

with that of a more recent primary open glaucoma study (60) , whilst has not been associated with IOP (61, 62) (the most powered of all glaucoma related GWAS). The *PLCE1* gene encodes for the phospholipase C epsilon 1. It is very strongly expressed in the retina, where PLCE1 has been suggested to regulate neuronal intracellular calcium levels and hence impacting growth and differentiation (63). Although the glaucoma and RD epidemiological associations could stem from glaucoma developing secondary to a retinal detachment operation, a high proportion of glaucoma has been reported, 9.5%, amongst patients undergoing primary operation for retinal detachment (64). Our data gives support to the latter' implications of shared genetic predispositions.

The partitioning of variants based on their effects across traits is a very powerful tool to better understand and separate disease pathological pathways contributing to their aetiologies. For this approach to be thorough and successful, it is clear that well powered studies are needed and for retinal detachment expanding the size of the study will be essential. With our study results largely driven by the availability of self-report and linked hospital records in UK Biobank, future expansion making use of new incident cases over time, the increased health records linkage, and the availability of similar datasets worldwide is a very promising way forward.

Materials and Methods

Ethics statement. All cohorts studied were approved by Research Ethics Committees as detailed below and all participants gave written informed consent. The UK Biobank study was conducted with the approval of the North-West Research Ethics Committee (Reference: 06/MRE08/65). Generation Scotland Scottish Family Health Study (GS:SFHS) has Research Tissue Bank status from the Tayside

Committee on Medical Research Ethics (REC Reference: 15/ES/0040). The Scottish rhegmatogenous retinal detachment (RRD) study was approved by the Research Ethics Committee (MREC-06/MRE00/19) and the Moorfields RRD collection by Research Ethics Committee (10/H0703/97).

Evaluation of retinal detachment self-report in UK Biobank. The criteria for self-reported retinal detachment (SR_RD) cases and controls based on the UK Biobank questionnaires are detailed in S2 Text. Proportions for conditions well documented to be associated with rhegmatogenous retinal detachment (RRD) were compared in cases and controls using a two-sided two-proportion z-test. Overlap with RD cases (ICD_RD) defined by relevant international classification of disease (ICD) codes from UK National Health Service (NHS) hospital patient records transcripts were examined. ICD codes relating to retinal detachment were ICD9 code 361 “retinal detachments and defects” and ICD10 codes H33 “retinal detachments and breaks”. In total 4777 (N=3913 ICD_RD and N=864 SR_RD with no available hospital record of detachment) were identified.

Case-control datasets for genome-wide association analysis (GWAS)

UK Biobank sets

All analyses were restricted to the large subset of participants with genotype data passing quality control and indicative of white-British ancestry (Supplementary Notes).

Retinal detachment

In the primary analysis, participants with retinal detachment ascertained from self-report or linkage to hospital records were combined (RD-SR_ICD) as cases. Controls were participants who had declared not to have any contraindication for undergoing spirometry (as used in the evaluation of retinal detachment self-report), were not cases, and had not self-reported a history of retinal operation/vitreectomy. The discovery GWAS comprised N=3977 cases and N=360,233 controls; 10,000 controls recruited in the London centres of Barts, Croydon and Hounslow were not included in this analysis and used as independent controls in the analysis of the clinically ascertained RRD cases from the Moorfield collection.

The case:control ratio for the discovery retinal detachment analysis was therefore 1:91. GWAS was additionally performed using a more balanced 1: 3 case/control ratio for comparison, with controls matched to cases on gender and assessment centre. As effect sizes and P-values are influenced by the case/control ratio, a 1:10 ratio was also analysed for the look-up of UK Biobank top results in the clinically ascertained RRD cohorts results and their meta-analysis so that identical case/control ratio were compared or pooled together.

High myopia

N= 2737 high myopia cases (spherical equivalent refraction (SER) greater than -6 Diopters) and N=47635 controls (case:control ratio 1:17.4- Supplementary Notes), were contrasted.

Cataract operation

N= 21,679 cases and N=387,283 controls (Supplementary Notes-case:control ratio 1:17.9) were analysed.

Clinically ascertained RRD cases and population-based controls

Scottish set

980 cases from the Scottish RRD study and 9,705 population-matched controls from GS:SFHS not linked to a retinal detachment operation (Supplementary Notes-case:control ratio~1:10) were analysed. 1,136,421 variants with high imputation quality ($INFO \geq 0.8$) and $MAF > 1\%$ following genotyping analyses detailed in the Supplementary Methods were tested.

London set

1184 cases recruited in London Moorfields eye hospital (Supplementary Notes) and 10000 gender matched London centres recruited UK Biobank controls, defined as per UK Biobank analysis of RD, were analysed. In total, 4,727,220 variants with high imputation quality ($INFO \geq 0.9$) and $MAF > 1\%$ following genotyping analyses detailed in the Supplementary Methods were tested.

Genome-wide association testing. Single variant GWAS was performed by testing for an additive effect at each reference allele within a linear mixed model to account for population relatedness and geographic structure. All analyses apart from one were performed using BOLT_LMM v1.3 (43, 65) which implements fast parallelised algorithms to analyse large ($N > 5000$) datasets. The London RRD set analysis was run using GCTA(35) as low heritability estimation prevented BOLT_LMM v1.3 from carrying out the genome scan. Polygenic contribution to trait can be modelled using a mixture of Gaussians priors on SNP effect sizes (default model allowing uneven effect sizes) or a single-Gaussian prior (standard infinitesimal model) in BOLT_LMM v1.3. Reported association p-values are those obtained for the default BOLT_LMM model but all were identical or very close to those obtained under the standard

infinitesimal model in our analyses. Covariates in the models were age (coded as 5 consecutive year of birth bins) and sex, and in addition, for the UK Biobank dataset, recruitment centre, genotyping array, genotyping batch and the 10 first components of the centrally performed UK Biobank principal components analysis. Only common to low frequency, $MAF > 1\%$, variants, were analysed given the small size of the case samples and the risk of false positive associations for rarer variants in the unbalanced case:control samples analysed. In the UK Biobank dataset, recent simulations from the BOLT-LMM developers (43) show no inflation of type 1 error, for a significance threshold α of $5 \cdot 10^{-8}$, at this MAF threshold with case fraction of 1% or higher.

Individual RD studies (each using a 1:10 case control ratio to harmonise effect sizes) summary statistics were meta-analysed using the inverse variance fixed effect scheme implemented in the software METAL(66). Variants with Cochran's Q-test heterogeneity of effect greater than 75% were filtered out.

Effects size on the observed scale were converted to $\log(\text{ODDS ratio})$ following formula described in Pirinen et al(67).

Replication. Replication analysis of 11 loci was performed using self-reported data from a GWAS including 9,171 cases and 406,168 controls of European ancestry, filtered to remove close relatives, from the 23andMe, Inc. customer database. All individuals included in the analyses provided informed consent and answered surveys online according to the 23andMe human subject protocol, which was reviewed and approved by Ethical & Independent Review Services, a private institutional review board (<http://www.eandireview.com>). Cases were defined as

those who reported either retinal tears or retinal detachment; controls were defined as those who reported not having either retinal tears or retinal detachment.

All 11 variants assessed for replication were imputed in this study and were among the 21,747,472 variants passing quality control in the GWAS. Association test results were computed using logistic regression assuming additive allelic effects, including age, sex, the top five principal components of ancestry, and genotyping platform as covariates in the model.

GWAS evaluation. Manhattan plots were drawn using the qqman library in R, and QQ plots using a local function. Regional association plots were plotted using LocusZoom: <http://locuszoom.sph.umich.edu/>. Inflation of type 1 error not accounted for by polygenicity was estimated using the LD score regression intercept (28) computed by the LDSC software. Z-scores calculated from the GWAS summary statistics from genotyped and well imputed (INFO ≥ 0.8) variants were regressed on pre-calculated LD scores (of European ancestry from the 1000G phase 1 reference panel). For one GWAS, the Scottish RRD set, the ratio $(intercept - 1)/(mean(\chi^2) - 1)$, which measures the proportion of the inflation in the mean χ^2 that the LD Score regression intercept ascribes to causes other than polygenic heritability was greater than 20% and the LD score regression intercept was used as inflation factor to apply genomic control on the results(68).

Manually, a locus was defined as a region with significant variants within a 500kb region centred on the lead variant (that of the lowest P-value in the region) and contiguous loci merged. Adjacent “loci” with variants displaying LD measure $r^2 > 0.1$ across loci, e.g HLA region for cataract operation GWAS, were merged into one

locus. GWAMA loci were defined and annotated within FUMA with the default clumping procedure (first clumping parameter $r^2 = 0.6$, second $r^2 = 0.1$) unless for finemapping investigation ($r^2 = 0.1$ for both clumping) to define larger regions.

Independent signals detection and Finemapping

The loci were investigated using GCTA v1.91.4beta for stepwise variable selection and conditional and joint (COJO) analyses using a subset of data including ~10000 white-British UK Biobank participants as reference for linkage disequilibrium patterns. GWAMA results, or the conditional analyses results for the region identified with more than one independent lead, were used to calculate approximate Bayes factor (abf) using Wakefield's formula (69), as implemented in the R package gtx v.2.0.1. Following Mahajan et al (36), the posterior probability for a variant to drive association (PPA) was then calculated as the abf of the variant divided by the sum of the abfs in the region. The 99% credible sets of a region were derived by summing the posterior probabilities in descending order until the cumulative posterior probability was >99%.

Fine-mapping was also performed, on the three loci identified in the discovery GWAS, using FINEMAP v1.3.1(37). This software uses shotgun stochastic search algorithm to identify the most likely causal configurations of the region. Each variant within a found credible set is defined by its posterior inclusion probabilities (PIP) of being causal and its $\log_{10}BF$ (Bayes factor) which quantifies the strength of causality evidence.

Myopia genetic risk score

A myopia genetic risk score (GRS) was derived from 71 out of 140 genome-wide significant lead variants for refractive error ($P \leq 5 \times 10^{-8}$) from a large-scale meta-analysis of studies (CREAM and 23andMe meta-analysis) (31) independent from our discovery studies. The 71 variants passed QC in our three investigated cohorts and are listed in Table S17. The GRS was constructed as the sum of the additive imputed dosage of the alleles increasing myopic refractive error, weighted by their effect on refractive error. Effect on retinal detachment risk was assessed using logistic regression with the following covariates: Year of birth bin, sex, assessment center, batch, genotyping array and 5 first PCs. The analysis using UK Biobank participants was restricted to those unrelated within the white-British ancestry subset (pairwise kinship coefficients lower than 0.0313).

Functional annotation and gene mapping

Functional annotation was performed using FUMA (34) v1.3.5, a recently developed integrative tool leveraging information from many biological data repositories.

FUMA heuristically defines independent lead SNPS within loci if they are in low LD $r^2 < 0.1$ (here using the UK Biobank White British set as reference panel). These variants, as well as those, tested or not, in high LD ($r^2 \geq 0.6$) with them in the reference panel, were annotated for predicted protein-altering or regulatory features following annotations from ANNOVAR, 2017-07-17 update, (<http://annovar.openbioinformatics.org>), RegulomeDB (<http://www.regulomedb.org/>), eQTL repositories (with note that none is available as yet for eye tissues) and the ChromHMM predicted 15 core chromatin states derived from ENCODE and ROADMAP repositories. SNP-trait known associations from the GWAS catalogue (e96_r2019-05-03) were also part of FUMA annotations. The SNP2GENE function

in FUMA identified putative target genes in an exhaustive manner: by physical mapping to the loci physical locations which are defined liberally by variants coordinates in high LD (>0.6) with any lead and “independent significant” variants which display medium LD with the lead variants (r^2 between 0.1 and 0.6), or based on genes whose expression has been significantly associated with those GWAS variants. eQTL repositories used include GTEx v6 and v7, BIOS QTL browser and BrainSpan amongst others.

Gene based analysis and Gene-set analysis

These analyses were performed using MAGMA v1.07 (70) within FUMA. Gene-based P-values are derived from an approximation of the sampling distribution of the mean of the χ^2 statistic for the SNPs in a gene, with gene coordinates that from NCBI 37.3 and LD pattern to account for dependency of SNPs P-values that of the UK Biobank White British reference data as input parameters. Genome-wide threshold of significance for the gene-based p-values was set to 2.68×10^{-6} , following Bonferroni correction for the $N=18625$ genes evaluated.

Gene-based P-values converted to Z values and a between-gene correlation matrix are used as input to perform gene sets enrichment tests. (70). These tests are based on expectation of an hypergeometric distribution for the null hypothesis of no enrichment. The raw p-values are adjusted following the Benjamini and Hochberg procedure (FDR set at 5%) to account for multiple testing within each gene-set categorie. Predefined gene sets from the molecular signatures database MsigDB v6.1 (<http://software.broadinstitute.org/gsea/msigdb>) were used.

Traits Heritability and genetic correlations

The heritability attributable to the joint contribution of genetic variants tagged by the common variants tested, h_g^2 , can be calculated using the variance components estimates from the models fitted to perform the GWAS. It was converted to a case:control ratio-independent heritability, on the scale of liability, h_{gl}^2 using the formula (1) discussed in(71) or (2) when controls were also selected using a trait threshold(72) for the analysis of high myopia)

$$(1) h_{gl}^2 = h_g^2 \times \frac{K(1-K)}{z^2} \times \frac{K(1-K)}{P(1-P)}$$

$$(2) h_{gl}^2 = \frac{h_g^2}{P(1-P) \left(\frac{z_U}{K_U} + \frac{z_L}{K_L} \right)^2}$$

where P is the prevalence of the binary trait in the analysed sample (e.g for the largest retinal detachment analysis in UK Biobank: $3977/(360233+3977)=1.1\%$), K the prevalence in the population of matching age group as that of the UK Biobank population. We made the assumption that conditions' prevalences in the UK Biobank sample are similar to that of the UK population; for retinal detachment, assuming $K=P$ was close to a previous UK RRD estimate of incidence of 12 per 100,000 population-year(4) with median age of 59 year old in the sample. For high myopia, cases corresponded to the 3.76% upper tail of the refractive error distribution and controls to the 65.5% lower tail. z^2 is the squared ordinate of a standard normal curve at the K quantile.

h_g^2 and h_{gl}^2 were also estimated using the linkage-disequilibrium (LD) score regression method(28). Genetic correlations (r_g) were those obtained by regressing the product of test statistics against LD-score(30) as implemented in the LDSC software.

GWAS look-up

Four GWAS results repositories were used: the GWAS catalogue (e96_r2019-05-03), PhenoScanner (as of September 2019) the Global Biobank Engine, Stanford, CA (URL: <http://gbe.stanford.edu>) (GBE) [March 2018] and the GeneATLAS, University of Edinburgh (URL: <http://geneatlas.roslin.ed.ac.uk/>) [March 2018]. In the Global Biobank Engine, over 2000 UK Biobank traits (including retinal detachment defined as in our discovery analysis) have been analysed in a first broad brush pass, on 337,000 unrelated participants of white British ancestry. The analysed traits include traits measured in smaller subsets of individuals in recall assessments, including the ophthalmologic assessment (e.g refractive error as a quantitative trait is analysed for N=82,752 participants). The GeneATLAS shows GWAS results for 778 traits measured in the complete set of UK Biobank participants of white British ancestry, using both related and unrelated individuals; results for the genotyped variants can be queried using the web interface.

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Data availability: Summary GWAS statistics for the retinal detachment GWAMA presented here are available from the University of Edinburgh Digital Repository DataShare: (<https://datashare.is.ed.ac.uk/handle/10283/3511>); summary GWAS statistics for individual UK-Biobank trait (high myopia, cataract operation and RD-SR-ICD) are returned to the UK-Biobank.

Web Resources

URLs. UK Biobank Access Management System, <http://www.ukbiobank.ac.uk/register-apply/>; HRC variants, <http://www.haplotype-reference-consortium.org/site>; LocusZoom: <http://locuszoom.sph.umich.edu/> ; NHGRI-EBI catalog of published genome-wide association studies, <http://www.ebi.ac.uk/gwas/>; Phenoscanner, <http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner>; LDSC, <https://github.com/bulik/ldsc>; BOLT, <https://data.broadinstitute.org/alkesgroup/BOLT-LMM/>; FUMA, <http://fuma.ctglab.nl/>; GCTA, <https://cnsgenomics.com/software/gcta/>; gtx, <https://github.com/tobyjohnson/gtx>; Haploreg, <http://archive.broadinstitute.org/mammals/haploreg/haploreg.php>; LD calculation tool, https://www.ensembl.org/Homo_sapiens/Tools/LD/, CADD pre-calculated scores, <http://cadd.gs.washington.edu/>; GTEx portal, <https://gtexportal.org/home/>

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Legends to Figures

Fig 1. Distribution of “retinal detachments and breaks” ICD10 code H33 subtypes amongst UK-Biobank participants. H33 encompasses subclasses H33.0 (retinal detachment with retinal break), H33.1 (retinoschisis and retinal cysts), H33.2 (serous retinal detachment), H33.3 (retinal breaks without detachment), H33.4 (traction detachment of the retina) and H33.5 (other retinal detachments). The numbers represent the UK Biobank participants (no filtering-all ethnicities included) associated with each code; as only overlap between two codes can be represented, individuals linked to more than 2 codes are counted several times. The plot was drawn with the R package *circlize* v0.4.3(73).

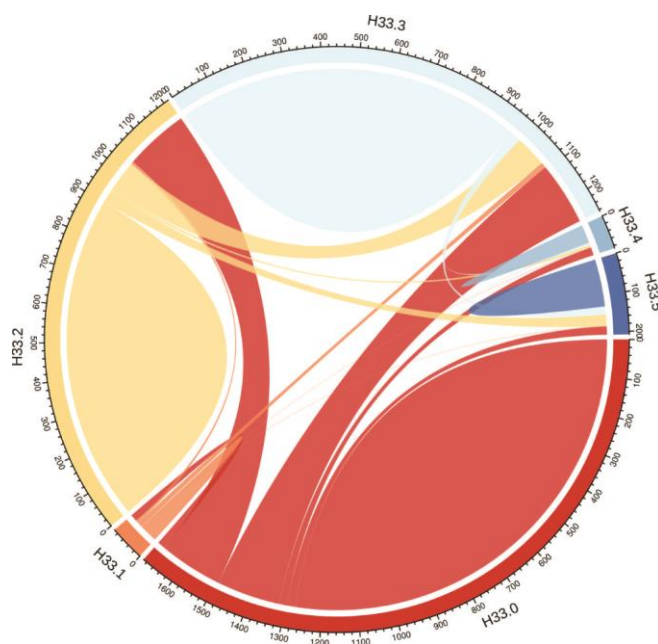


Fig 2. Regional association plots at the three genome-wide significant loci in the primary UK Biobank retinal detachment analysis across different case definitions. The y axis represents the negative logarithm (base 10) of association P-value and the x axis the position on the chromosome. The lead variants from the RD-SR-ICD discovery study (A - Ncases=3977) are marked by a purple diamond. The colours of the other variants reflect LD strength (r^2) with the lead variant at each locus. (B): results at the same loci when cases linked to ICD10 codes H33.1 and H33.3 are omitted (Ncases=2893). (C): results when cases are restricted to participants with H33.0 code (Ncases=1380).

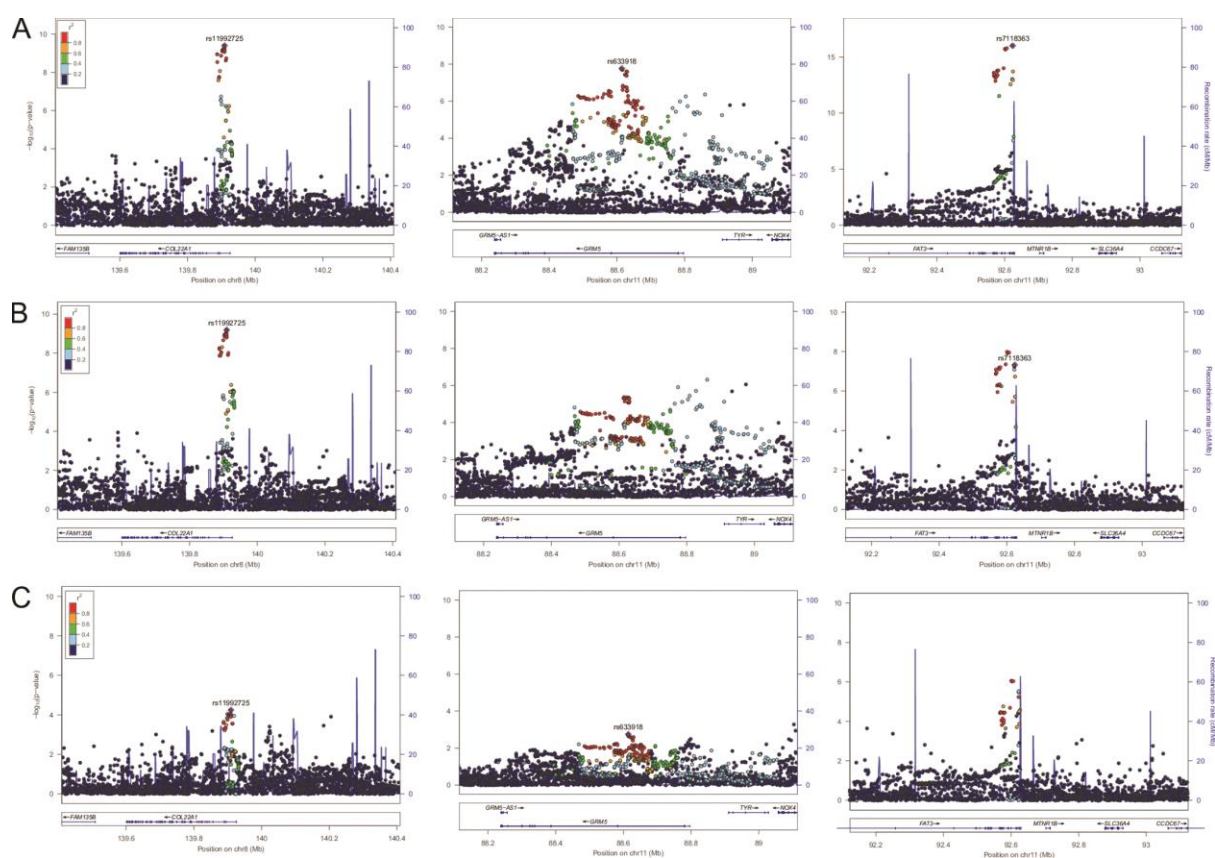


Fig 3. Myopia genetic risk score effect on retinal detachment risk using UK Biobank RD-SR-ICD cases or clinically ascertained RRD cases. The effects of consecutive myopia genetic risk score (GRS) quintile on retinal detachment (RD-SR-ICD) risk in UK Biobank and on Rhegmatogenous RD (RRD) risk in the aggregated clinically ascertained sets are displayed in black and grey bars respectively. Quintiles were calculated using N=408972 UK-Biobank participants of white-British ancestry. Odds-ratio for detachment, plotted along the y axis, uses odd in the first quintile as the reference. GRS boundaries for each quintile are given SFig6. Error bars denote the odds ratio 95% confidence interval.

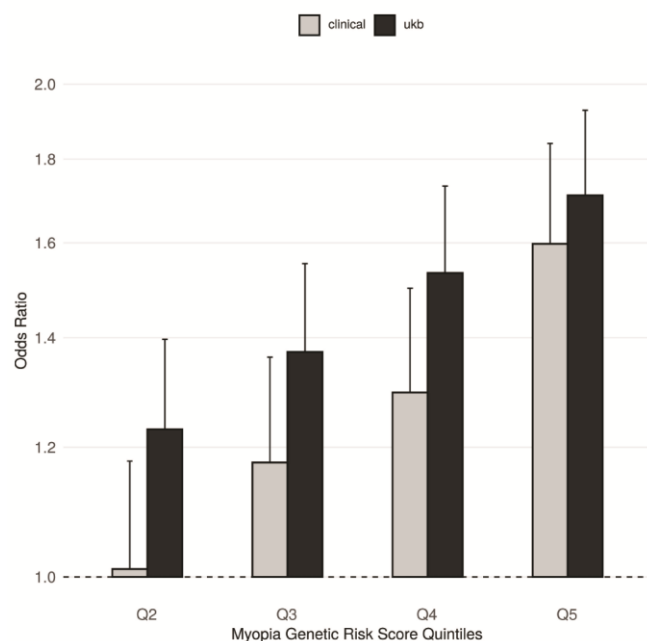
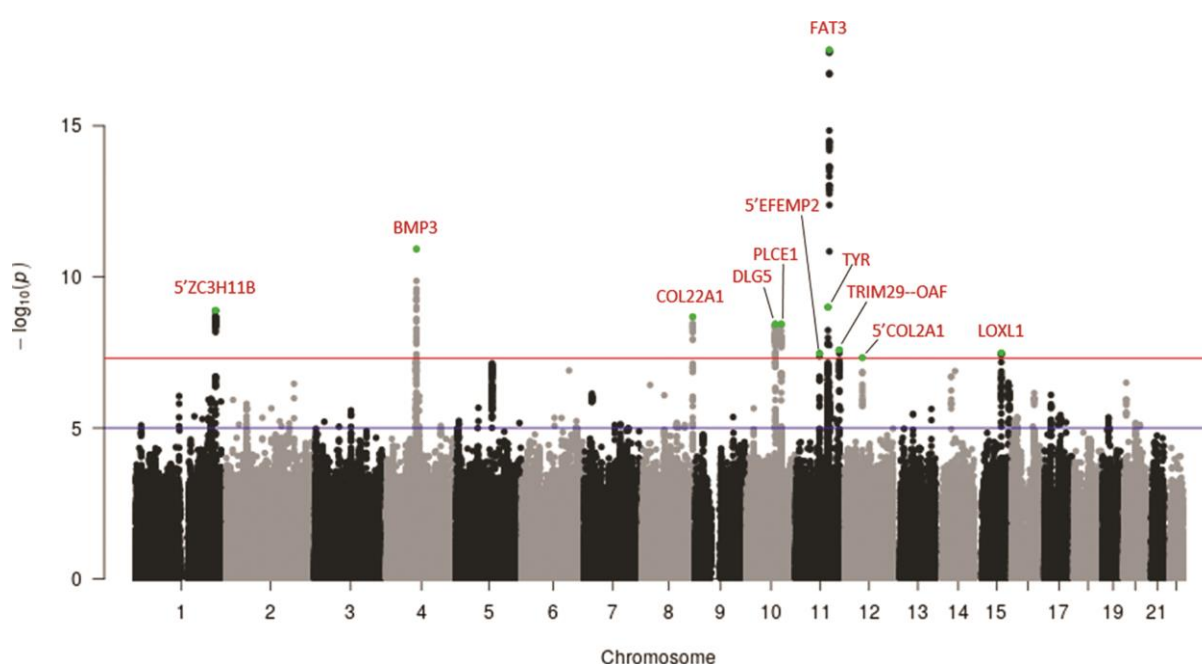


Fig 4. Manhattan plot following meta-analysis of genome-wide association studies using UK Biobank cases (RD-SR-ICD, N=3977) and clinically ascertained RRD cases (N=2164). The y axis represents the negative logarithm (base 10) of the meta-analysis P-values and the x axis the location of variants tested. Loci displaying association reaching the genome-wide significant threshold (red line, $P < 5 \times 10^{-8}$) are indicated in red, with lead variant (lowest P-value within a locus) indicated in green. Suggestive level of significance ($P < 10^{-5}$) is indicated by a blue line.



Tables

Table 1. Self-reported features in self-reported retinal detachment cases and controls in UK Biobank (all ethnicities).

		RD-SR N=1754	RD-SRwithOP N=1391	Controls N=457255
% female (ratio female/male)		40.94%** (718/1036=0.69)	39.76%** (553/838=0.66)	54.84% (250773/206482=1.2)
Year of birth [med;min-max]	all	1947;1937-1969	1947;1937-1969	1951;1934-1971
	Male	1947;1937-1969	1947;1937-1969	1950;1934-1971
	Female	1947;1937-1968	1948;1938-1968	1951;1936-1970
Cataract N (%)		533 (30.39%)**	449 (32.28%)**	6856 (1.50%)
% amongst Female/Male		29.67%**/30.88%**	32.55%**/32.10%**	1.62%/1.36%
Cataract op N (%)		456 (26.00%)**	383 (27.53%)**	4291 (0.94%)
% amongst Female/Male		25.49%**/26.35%**	27.31%**/27.68%**	0.89%/1.00%
Eye trauma N (%)		25 (1.43%)**	21 (1.51%)**	553 (0.12%)
% amongst Female/Male		0.56%**/2.03%**	0.54%**/2.15%**	0.06%/0.19%
T2D N (%)		24 (1.37%)**	23 (1.65%)**	3302 (0.72%)
% amongst Female/Male		0.97%NS/1.74%*	1.27%**/1.91%**	0.51%/0.97%
T1D N (%)		6 (0.34%)**	6 (0.43%)**	404 (0.09%)
% amongst Female/Male		0.42%**/0.29%NS	0.54%**/0.36%*	0.08%/0.10%
Diabetic-eye disease N (%)		7 (0.40%) NS	6 (0.43%)NS	1063 (0.23%)
% amongst Female/Male		0.14%NS/0.58%NS	0.18%NS/0.60%NS	0.16%/0.32%
Glaucoma N (%)		126 (7.18%)**	105 (7.55%)**	4771 (1.04%)
% amongst Female/Male		6.41%**/7.72%**	6.51%**/8.23%**	0.91%/1.21%
Macular degeneration N (%)		9 (0.51%)**	5 (0.36%)**	348 (0.08%)
% amongst Female/Male		0.84%**/0.29%**	0.72%**/0.12%NS	0.09%/0.06%
age_at first use of corrective lens for myopia [med; min-max]		12; 1-55	12; 1-50	17; 1-68

RD-SR are UK Biobank participants who self-reported a retinal detachment, RD-SRwithOP additionally self-reported to have undergone a retinal operation. Controls are described in Supplementary Note 2. ** and * denotes significant difference compared to control proportion based on a two sided proportion z test at respectively 1% and 5% threshold; NS not significant difference. Med: median, Min: minimum, Max:Maximum, Op:operation

Table 2. Look-up of retinal detachment GWAMA associations in the 23andMe dataset

SNP	Locus	EA	ALT	EAF	RD GWAMA		RD 23andMe	
					OR[CI]	P	OR[CI]	P
rs4373767	5' ZC3H11B	T	C	0.63	1.128 [1.086-1.171]	1.30E-09	1.045 [1.014-1.077]	4.03x10⁻³
rs74764079	BMP3	T	A	0.97	0.717 [0.642-0.802]	1.20E-11	0.825 [0.755-0.901]	3.02x10⁻⁵
rs11992725	COL22A1	G	A	0.32	1.125 [1.082-1.170]	2.10E-09	1.110 [1.076-1.146]	7.05x10⁻¹¹
rs1248634	DLG5	G	A	0.71	0.888 [0.854-0.942]	3.67E-09	0.974 [0.942-1.007]	0.122
rs11187838	PLCE1	G	A	0.57	0.894 [0.861-0.928]	3.64E-09	0.9397 [0.912-0.968]	4.51x10⁻⁵
rs7940691	5' EFEMP2	T	C	0.36	1.113 [1.072-1.155]	3.50E-08	1.005 [0.974-1.037]	0.766
rs1042602	TYR	C	A	0.63	0.888 [0.856-0.922]	1.01E-09	0.9499 [0.921-0.9798]	1.17x10⁻³
rs10765567	FAT3	T	A	0.37	0.841 [0.810-0.873]	3.13E-18	0.874 [0.847-0.901]	1.64x10⁻¹⁷
rs11217712	TRIM29---OAF	T	G	0.31	0.892 [0.857-0.927]	2.65E-08	0.970 [0.939-1.002]	6.73x10 ⁻²
rs9651980	5' COL2A1	T	C	0.087	1.188 [1.114-1.267]	4.72E-08	1.052 [0.997-1.110]	6.01x10 ⁻²
rs4243042	LOXL1	T	A	0.47	0.889 [0.854-0.925]	3.33E-08	0.990 [0.961-1.020]	0.519

EA is the allele on the plus strand for which the effect is reported, ALT the alternate allele, EAF is the effect allele (EA) frequency in the meta-analysis. Effects obtained from linear mixed models (RD GWAMA) or logistic regression (23andMe) are reported as odds ratio (OR) for retinal detachment and P is the pvalue. CI: 95% confidence interval. In bold, significant replication.